REMARKS

Claims 6-19, 22 and 24-41 were pending in the subject application. By this Amendment claims 6-13, 24 and 34-41 have been canceled. Claims 14, 15, 27 and 28 have been amended. Upon entry claims 14-19, 22 and 25-33 are pending and under examination.

Support for claim 14 as amended may be found, *inter alia,* at paragraphs [0028] and [0029] and [0009]. Support for claims 15, 27 and 28 as amended may be found, *inter alia,* in original claims 15, 27 and 28. Applicants maintain that the amendments do not raise an issue of new matter. Entry of the amendments is respectfully requested.

STATUTORY DOUBLE PATENTING REJECTION

Claims 6-19 and 22-41 have been provisionally rejected under 35 U.S.C. §101 as allegedly claiming the same invention as claims 1-33 of copending Application No. 11/841,489. The rejection is respectfully traversed.

Claims 6-13, 23, 24 and 34-41 have been canceled. Claims 14 and 15 have been amended. Claims 15-18 and 25 depend from amended claim 14. Therefore the rejection has been overcome with respect to claims 6-18, 23-25 and 34-41. Applicants undertake to either cancel or amend claims of the '489 application to eliminate any statutory double patenting.

OBVIOUSNESS-TYPE DOUBLE PATENTING

Claims 19, 22 and 26 have been provisionally rejected on grounds of alleged obviousness-type double patenting over claims 1-5 of copending Application No. 11/844,431 (the '431 application) and claims 1, 6-7, 9-10, 15, 22-2 of copending Application No. 11/844,432 (the '432 application).

The rejections are respectfully traversed. The '431 application and the '432 application were filed after the subject application. Accordingly, upon an indication of otherwise allowable subject matter the provisional obviousnesss-type double patenting rejections should be withdrawn and the subject application should be allowed to issue as a patent without a terminal disclaimer. MPEP §804(I)(B)(1), Rev. 5, Aug. 2006, page 800-17, right column.

INVENTION IS NOVEL OVER HAIGH

Claims 6, 10-14, 18-19, 27, 32-34 and 39-41 have been rejected under 35 U.S.C. §102(b) as allegedly being anticipated by U.S. Patent No. 5,589,492 (Haigh). Claims 6, 10-13, 34 and 39-41 have been canceled. As applied to claims 14, 18, 19, 27, 32 and 33 this rejection is respectfully traversed.

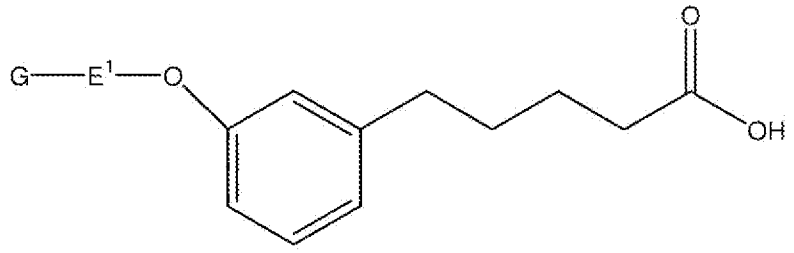
Claims 14 and 18 are directed to compounds in which "A" is substituted phenyl or substituted or unsubstituted cycloalkyl. Claims 19 and 32 are directed to compounds in which "A" is 2,6-dimethylphenyl. Claims 27 and 33 are directed to compounds in which "A" is substituted phenyl.

Referring to the nomenclature of the subject application, Haigh discloses certain compounds in which "A" is a heterocycle. In contrast, in the pending claims "A" is not a heterocycle. Applicants respectfully submit that the anticipation rejection over Haigh has been overcome.

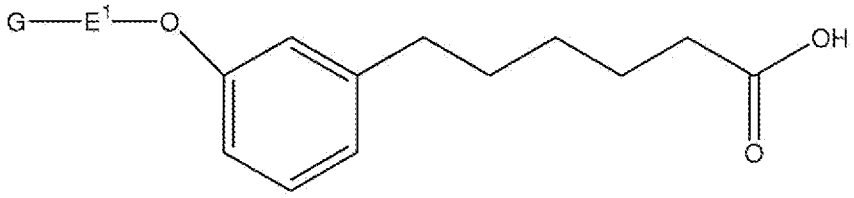
INVENTION IS PATENTABLE OVER TAJIMA

Claims 6-19, 22 and 24-41 have been rejected under 35 U.S.C. §102(b) as allegedly anticipated by or, in the alternative, under 35 U.S.C. §103(a) as allegedly obvious over WO 99/11255 (Tajima et al.). Claims 6-13, 24 and 34-41 have been canceled. As applied to claims 14-19, 22 and 25-33, this rejection is respectfully traversed.

Tajima discloses two subgenuses that overlap with the compounds claimed in the subject application, as follows:



(Iaa-2)



(Iaa-3)

G is:

1) carbocyclic group; or

2) heterocyclic group; and

The carbocyclic group and heterocyclic group in said G group may be substituted by one to four substituents selected from the group consisting of:

(i) C1 - C8 alkyl group;

(ii) C1 - C8 alkoxy group;

(iii) halogen atoms;

(iv) trifluoromethyl group; and

(v) nitro group,

E^1 is:

1) single bond;

2) C1 - C8 alkylen group;

3) C2 - C8 alkenylen group; or

4) C2-C8 alkynylen group.

(Formulas Iaa-2 and Iaa-3 taken from pages 33 and 34, respectively. Definitions of G and E^1 translated from claim 1).

The Tajima subgenuses are written in Markush format and each encompasses tens of thousands of compounds. They overlap the compounds claimed by applicants, if one selects certain values for variable substituents from a large group of possibilities.

For compounds in which G-E^1 is substituted phenylalkyl or (cycloalkyl)alkyl, none of the compounds exemplified in the reference contains phenyl substituted by halo, alkyl having 1 or 2 carbon atoms, perfluoromethyl, alkoxy having 1 or 2 carbon atoms, or perfluoromethoxy; or cycloalkyl that is unsubstituted or in which one or two ring carbons are mono-substituted by methyl or ethyl. The closest Tajima compounds are compounds 1, 2 and 3 on page 33; compounds 1, 2 and 3 on page 34; the compounds illustrated on the bottom of pages 82 and 90, on page 91, on the bottom of pages 94 and 98; on pages 101 and 128, on the top of page 131, and on the bottom of page 137. To the extent that Tajima's preferences can be discerned from the exemplified compounds, when G is phenyl the preferred substitution pattern is no substitution or mono-substitution and the preferred substituents are n-butyl, isobutyl and n-pentyl.

"The fact that a claimed compound may be encompassed by a disclosed generic formula does not by itself render that compound obvious." In re Baird, 16 F.3d 380, 382, 29 USPQ2d 1550, ____ (Fed. Cir. 1994), citing In re Jones, 958 F.2d 347, 350, 21 USPQ2d 1941, 1943 (Fed. Cir. 1992). Since "lack of novelty is the ultimate of obviousness" (In re Fracalossi, 681 F.2d 792, 794215 USPQ 569 (CCPA 1982)), it therefore follows that the fact that a claimed compound may be encompassed by a disclosed generic formula does not by itself render that compound anticipated.

As a general rule, a structural formula containing variables does not describe a subgenus or species in which it is necessary to pick and choose among possible values for more than one variable to arrive at the desired subgenus or species. At most such a formula can describe a subgenus or species in which it is necessary to limit no more than one variable to arrive at the desired subgenus or species. This can be seen from the case of In re Driscoll, which distinguished In re Ruschig, 379 F.2d 990, 154 USPQ 118 (CCPA 1967) (Ruschig II) based on this legal principle. In Ruschig II the court determined that a generic structure with two variables did not constitute a written description of an individual compound which could only be arrived at by selecting specific values for both variables. The structural formula in Ruschig II "could have described, at best, only a subgenus including the specific compound claimed and not the compound itself." In re Driscoll, 562 F.2d 1245, 1250, 195 USPQ 434, ___ (CCPA 1977). Accordingly the Tajima reference, at best, describes the subgenuses of Formula Iaa-2 and Formula Iaa-3 in which G is a carbocyclic ring substituted by 0, 1, 2, 3 or 4 C_{1-8} alkyl groups. However the reference does not describe a subgenus in which G is phenyl substituted by 1 or 2 groups selected from halo, alkyl having 1 or 2 carbon atoms, perfluoromethyl, alkoxy having 1 or 2 carbon atoms, and perfluoromethoxy; much less a subgenus in which G is phenyl substituted by 1 or 2 alkyl groups having 1 or 2 carbon atoms; and certain does not disclose a subgenus in which G is 2,6-dimethylphenyl. Nor does it describe any of the specific compounds claimed by applicants.

In stating that "the carbocyclic compound (i.e. phenyl;) can be substituted with up to four 1-8 alkyl groups" the rejection mischaracterizes the disclosure of the reference by implying that the terms "carbocyclic" and "phenyl" are just alternate ways of saying the same thing. They are not. The term carbocyclic is defined as "Any organic compound whose skeleton is in the form of a closed ring of carbon atoms. This includes both alicyclic and aromatic structures." (Hawley's Condensed Chemical Dictionary, 14th ed. (Wiley 2001), page 206. (submitted concurrently herewith). Thus the reference does not specifically disclose phenyl substituted by up to four C_{1-8} alkyl groups. It discloses only

carbocyclic substituted by up to four C_{1-8} alkyl groups, which is further from the subject matter of claims 15-19, 22 and 25-33 than what is implied by the rejection.

A limited exception to the general rule of Driscoll can be found in situations where the genus is so small that one can "at once envisage" each of its members. Such a situation existed in the case of In re Petering, 301 F.2d 676, 133 USPQ 275 (CCPA 1962). The prevailing jurisprudence considers Petering to have "involved a very special situation" (In re Ruschig, 343 F.2d 965, 973, 145 USPQ 274 (CCPA 1965) (Ruschig I)) in which what was special included "the disclosure of a small genus" of twenty compounds (Bristol-Myers Squibb Co. v. Ben Venue Laboratories, Inc., 246 F.3d 1368, 1380, 58 USPQ.2d 1508 (Fed. Cir. 2001)) and "the description of specific preferences" for the variables (Merck & Co., Inc. v. Biocraft Laboratories, Inc., 874 F.2d 804, 807, 10 USPQ.2d 1843 (Fed. Cir. 1989)). The importance of a small genus, after taking into account any preferences described in the prior art reference, is intimately related to the rationale of Petering. In Petering the court concluded that the person of ordinary skill in the art upon reading the prior art patent would, "at once envisage each member of this limited class." In re Petering, 301 F.2d 676, 681, 133 USPQ 275, ___ (CCPA 1962). Only with a small genus can one "at once envisage" each of its members.

The reference discloses two subgenuses, each of which encompasses tens of thousands of compounds. The reference does not disclose any preference for methyl or ethyl at any variable position when G is carbocyclic, and certainly does not disclose any preference for G being 2,6-dimethylphenyl. This is not the special situation in which the rule of In re Petering was intended to apply. Accordingly, the claims are not anticipated under 35 U.S.C. §102.

The claimed invention is not obvious over the cited reference. The subgenuses disclosed by Tajima each encompass tens of thousands of compounds. They overlap the compounds claimed by applicants, only if one selects certain values for variable substituents from a large group of possibilities.

The obviousness rejection depends, in part, on the incorrect allegation that Tajima allegedly states that "the carbocyclic compound (i.e. phenyl;) can be substituted with up to four 1-8 alkyl groups" the rejection mischaracterizes the disclosure of the reference by implying that the terms "carbocyclic" and "phenyl" are just alternate ways of saying the same thing. They are not. The term carbocyclic is defined as "Any organic compound whose skeleton is in the form of a closed ring of carbon atoms. This includes both alicyclic and aromatic structures." (Hawley's Condensed Chemical Dictionary, 14th ed. (Wiley 2001), page 206. (submitted concurrently herewith). Thus the reference does not specifically disclose phenyl substituted by up to four C_{1-8} alkyl groups. Rather, it discloses carbocyclic substituted by up to four C_{1-8} alkyl groups, which is more generic.

The rejection alleges that "to modify the substituted carbocyclic (i.e. phenyl) with 2 methyl groups at the 2nd & 6th position on the phenyl would have been within the skill of one of ordinary skill in the art." (November 1, 2007 Office Action). That allegation is correct in one respect but incorrect in another. If asked to make a compound in which G was phenyl substituted by 2 methyl groups at the 2- and 6- positions, making such a compound would have been within the skill of the person of ordinary skill in the art. But deciding to modify the Tajima compounds by substituting them with one or two methyl or ethyl groups, not have been obvious to the person of ordinary skill in the art. And it certainly would not have been obvious to modify the Tajima compounds by making the 2,6-dimethylphenyl analog.

For compounds in which G-E^1 is substituted phenylalkyl or (cycloalkyl)alkyl, none of the compounds exemplified in the reference contains phenyl substituted by halo, alkyl having 1 or 2 carbon atoms, perfluoromethyl, alkoxy having 1 or 2 carbon atoms, or perfluoromethoxy; or cycloalkyl that is unsubstituted or in which one or two ring carbons are mono-substituted by methyl or ethyl. The closest Tajima compounds are compounds 1, 2 and 3 on page 33; compounds 1, 2 and 3 on page 34; the compounds illustrated on the bottom of pages 82 and 90, on page 91, on the bottom of pages 94 and 98; on pages 101 and 128, on the top of page 131, and on the bottom of page 137. To the extent that

Tajima's preferences can be discerned from the exemplified compounds, when G is phenyl the preferred substitution pattern is no substitution or mono-substitution and the preferred substituents are n-butyl, isobutyl and n-pentyl.

In view of the large size of the Tajima subgenuses and the absence of preferences that would lead one to the claimed invention, the person of ordinary skill in the art would not have been motivated, either by the prior art or otherwise, to modify the Tajima compounds so as to arrive at the instant invention.

In view of the amendments and the preceding remarks, applicants respectfully submit that the anticipation and obviousness rejections over Tajima have been overcome.

CLAIMED INVENTION IS ENABLED

Claims 6-19, 22 and 24-41 have been rejected under 35 U.S.C. §112, first paragraph, as allegedly being based on a nonenabling disclosure. This rejection is respectfully traversed. Claims 6-13, 24 and 34-41 have been canceled. As applied to claims 14-19, 22 and 25-33 the rejection is respectfully traversed.

The rejection is based on the "how to use" requirement of Section 112, first paragraph. Compliance with the "how to make" requirement of Section 112, first paragraph, is not questioned.

The rejection is based on the position that the specification "does not reasonably provide enablement for treating all of the diseases listed in claim 6, 13-14, 34, 41 using any of these compounds". (November 1, 2007 Office Action, page 5). But the claims do not recite a list of diseases. Therefore even assuming for the sake of argument that the complete list of diseases referred to by the rejection is not enabled, the basis of the rejection still does not apply.

"[W]hen a compound or composition claim is not limited by a recited use, any enabled use that would reasonably correlate with the entire scope of that claim is sufficient to preclude a rejection for nonenablement based on how to use." MPEP §2164.01(c), Rev. 6, sept. 2007, page 2100-195, right column, last paragraph. See also In re Brana, 51 F.3d 1560, 34 USPQ.2d 1436 (Fed. Cir. 1995); Cross v. Iizuka, 753 F.2d 1040, 224 USPQ 739 (Fed. Cir. 1985); Application of Krimmel, 48 CCPA 1116, 292 F.2d 948, 130 USPQ 215 (1961). The pending claims are not limited by a recited use and it is undisputed that the specification provides an enabled use. Therefore a rejection for nonenablement based on how to use is improper.

The claims are directed to certain compounds and their salts (claims 19, 22 and 26-33) and to a pharmaceutical composition (claims 14-18 and 25). No claim recites a disease or a list of diseases. Accordingly, the claims are not limited by a recited use.

The rejection acknowledges that the specification is "enabling for reducing blood glucose, triglycerides and fatty acids level in diabetic mice using the compounds listed in claims . . . ." (November 1, 2007 Office Action, page 5). Accordingly the Office accepts that there is an enabled use.

Even if enablement of a whole list of diseases not recited in the claims would be needed to satisfy the enablement requirement of Section 112, first paragraph, the rejection would still be improper. In the instant case applicant has disclosed certain of compounds, has described how to make such compounds, has stated what diseases they are useful for treating, has taught how to formulate and administer such compounds, as well as their dosages. And yet the Office asserts its "position that one skilled in the art could not practice the invention without undue experimentation." (November 1, 2007 Office Action, page 6). In view of the extensive disclosure in this application, the rejection's assertion of undue experimentation presumably means that the Office does not believe that the compounds recited in the claims are useful in treating the diseases discussed in the specification when administered as described in the specification.

The Office bears the burden of establishing that an invention does not satisfy the enablement requirement of 35 U.S.C. §112, first paragraph. As stated by the CCPA in In re Marzocchi:

> "As a matter of Patent Office practice, then, a specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as in compliance with the enabling requirement of the first paragraph of § 112 unless there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support."

(In re Marzocchi, 439 F.2d 220, 223, 169 USPQ 367, ___(CCPA 1971)) (underlining added). It is not sufficient for the Office to simply assert that it doubts the correctness of the statements in the disclosure. The Office must back up its doubts with evidence or reasoning. Again from In re Marzocchi:

> "In any event, it is incumbent upon the Patent Office, whenever a rejection on this basis is made, to explain why it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement."

(In re Marzocchi, 439 F.2d at 224, 169 USPQ at ___ (CCPA 1971)) (internal citations omitted) (underlining added). The only reasoning presented by the rejection is the alleged unpredictability of the pharmaceutical art in general. The rejection stated:

> "It is generally recognized in the art that biological compounds often react unpredictably under different circumstances. The relative skill of the artisan or the unpredictability of the pharmaceutical art is very high."

(November 1, 2007 Office Action, page 7) (internal citations omitted). But that does not constitute adequate reasoning to support an enablement rejection. If the mere assertion

that the pharmaceutical art is unpredictable would be accepted as sufficient reasoning, it would mean that in the case of all biological and pharmaceutical inventions applicants would have the burden of demonstrating enablement rather than the Office having the burden of demonstrating that an invention is not enabled. And that would be contrary to the law as articulated in Marzocchi above.

The specification tested and demonstrated the activity of a representative number of compounds. The person of ordinary skill in the art would accept that other compounds within the genus would possess activity similar to the compounds tested.

The November 1, 2007 rejection singled out cachexia as a disorder whose treatment allegedly is not enabled by the specification. Compounds of the invention reverse insulin resistance associated with diabetes and metabolic disease. While insulin resistance is often associated with obesity (especially in the setting of concurrent hyperinsulinemia), insulin resistance is also a component of disease states involving weight loss (abstract of Wedick NM, et al. (2001) Insulin resistance precedes weight loss in adults without diabetes. American Journal of Epidemiology 153:1199-1205; abstract of Rofe et al., (1994) Altered insulin response to glucose in weight-losing cancer patients. Anticancer Research 14:647-650.) (submitted concurrently herewith).

Cachexia involves muscle wasting associated with disease states including cancer, systemic inflammation, infection and aging. A key element in cachexia is impaired insulin sensitivity, especially in muscle. Cancer patients with weight loss often have impaired glucose tolerance, a sign of insulin resistance (Rofe et al., 1994 (abstract); abstract of Tayek, (1992) A review of cancer cachexia and abnormal glucose metabolism in humans with cancer. Journal of the American College of Nutrition 11:445-456) (submitted concurrently herewith). Insulin signaling in muscle inhibits proteolysis; either insulin deficiency or insulin resistance disinhibits proteolysis, leading to loss of muscle mass. Combined insulin deficiency and resistance occurs in uncontrolled Type 1 diabetes and in cancer cachexia.

An additional link between insulin and body weight dysregulation in both obesity and cachexia is tumor necrosis factor alpha (TNFα). TNFα was originally known as "cachectin" due to its role in cachexia or muscle wasting and weight loss induced by infection and cancer. However, TNFα expressed in adipose tissue induces insulin resistance and obesity (abstract of Argiles et al., (1997) Journey from cachexia to obesity by TNF. The FASEB Journal 11:743-751) (submitted concurrently herewith). TNFα is one of the causes of insulin resistance in both diabetes and cachexia (abstract of de Alvaro et al., (2004) Tumor Necrosis Factor α produces insulin resistance in skeletal muscle by activation of Inhibitor κB Kinase in a p38 MAPK-dependent manner (2004) Tumor Necrosis Factor α produces insulin resistance in skeletal muscle by activation of Inhibitor κB Kinase in a p38 MAPK-dependent manner) (submitted concurrently herewith).

Compounds of the invention reverse insulin resistance associated with diabetes and obesity, and can attenuate weight gain in that situation. However, by addressing insulin resistance in situations where muscle wasting is occurring, including insulin deficiency states, compounds of the invention attenuate the severity of cachexia, both prophylactically and therapeutically.

In view of the foregoing applicants respectfully submit that the rejection under Section 112, first paragraph, has been overcome.

CLAIMS NOT INDEFINITE

Claims 6-13 and 34-41 have been rejected under 35 U.S.C. §112, second paragraph as allegedly being indefinite. This rejection is respectfully traversed. Claims 6-13 and 34-41 have been canceled. Accordingly the rejection is now moot and should be withdrawn.

CONCLUSION

In view of the amendments and the preceding remarks, applicants respectfully submit that the subject application is now in condition for allowance. Reconsideration and withdrawal of all rejections is respectfully requested.

No fee, other than the extension of time fee, is believed necessary in connection with the filing of this Amendment. If any additional fee is required, the Commissioner is hereby authorized to charge the amount of such fee to Deposit Account No. 50-1677.

Respectfully submitted,

/Lewis J. Kreisler/

Lewis J. Kreisler
Reg. No. 38522
Attorney for Applicant(s)

930 Clopper Road
Gaithersburg, MD 20878
Phone: (240) 631-2500 x3276
Facsimile: (240) 683-3794